UNIVERSITI PUTRA MALAYSIA

CELLULAR AND MOLECULAR CHARACTERIZATION OF ATHEROTHROMBOSIS-RELATED MARKERS IN SPRAGUE DAWLEY RATS FED WITH HIGH CHOLESTEROL DIET SUPPLEMENTED WITH HERBAL EXTRACTS

IBRAHIM KALLE KWAIFA

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By

IBRAHIM KALLE KWAIFA

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Doctor of Philosophy

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DEDICATION

This thesis is dedicated to Almighty Allah (SWT), who saved me, gave me health, strength and wisdom throughout the study period

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Doctor of Philosophy

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Chairman : Associate Professor Sabariah Md Noor, MD, MPath, AM
Faculty : Medicine and Health Sciences

Atherothrombotic cardiovascular diseases are the most common cause of death worldwide. Although antiplatelet, anticoagulant, simvastatin and other related drugs globally prescribed for these disorders have been available, some are commonly associated with several adverse effects. Intervention with natural-based preparation has been recognized as an alternative. This study utilised a combination of herbal extracts for the treatment of atherothrombosis in Sprague Dawley (SD) rats fed with a high cholesterol diet (HCD). The study investigated the therapeutic potentials of herbal extracts; a combination of *Zingiber officinale* (ginger), *Allium sativum* (garlic), *Citrus Limon* (lemon), *Malus Domestica* (Apple)/ apple cider vinegar and Honey (ZACAH) on cellular and molecular atherothrombosis-related markers in SD rats fed with HCD. Identification of the related phytochemicals present in ZACAH extracts was performed by ultra-high performance liquid chromatography-mass spectrophotometry (UHPLC-MS) profiling at both negative and positive models. Thirty-six male SD rats were randomly divided into six groups. The normal diet (ND), HCD, treatment with simvastatin (TRTSM) at 10mg/kg of body weight (BW), treatment with ZACAH extracts (TRT1) at 1mg, 3mg (TRT2), and 5mg (TRT3) per kilogram of BW. At the end of the 12 weeks of experiments, the rats were sacrificed, and the collected blood was subjected to serum lipid profile, protein expressions, and platelet ultrastructural analysis by scanning electron microscope (SEM). The atherogenic index (AI) and % protection were calculated based on the results obtained from the lipid profile. SEM was also used to examine the aorta endothelial ultrastructural changes. The aorta and liver tissues were utilised for histopathological examinations by haematoxylin & eosin (H & E) and Masson's trichrome (MT) stains. The tissues were also processed for the mRNA expression profiling of lipid metabolism atherothrombosis-related genes, endothelial prothrombotic and coagulation related genes, and the genes of the fibrinolytic system. Ten related phytochemical compounds present in ZACAH extracts were identified, including gingerol (retention time (RT); 18.62, compounds %; 5.6), hesperidin (11.19,

12.1), naringin (10.07, 13.1), sulindac (13.96, 9.7), scoparone (15.86, 8.0), hesperetin (11.18, 12.1), rutin (9.90, 13.2), limonin (17.87, 6.2), carboxylic acid (3.30, 18.9) and citric acid (2.18, 20). Increased BW and food intake were recorded in all the experimental groups, while a significant difference was observed in the HCD group compared to ND, TRTSM and ZACAH extracts treatment groups (p<0.05). The total cholesterol (TC), triglycerides (TG) and low-density lipoprotein (LDL) levels were significantly increased, and a decrease in high-density lipoprotein (HDL) was observed in the HCD group compared to ND, TRTSM and ZACAH extracts treatment groups (p<0.05). Significant differences were observed in the AI of HCD compared to ND and ZACAH extracts treatment groups (p<0.05). The % protection was improved at TRTSM (18%), TRT1 (55.6%), TRT2 (59.7%), and TRT3 (72.8%) in dose-dependent manner. The SEM analysis revealed organized atherothrombosis, smooth muscle cells proliferation in the intima, and significantly activated platelets in the HCD group. Histopathological examinations revealed a significant increase in the intima-media ratio, marked increase in collagen fibres and intense hepatic steatosis in the HCD group compared to ND, TRTSM and ZACAH extracts treatment groups (p<0.05). The mRNA expression of lipid metabolism genes, including 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMG-CoA-R), proprotein convertase subtilizing Kexin-9 (PCSK-9) and sterol regulatory element-binding protein-2 (SREBP-2) were upregulated while the expression of low-density lipoprotein-receptor (LDL-R) gene was downregulated in the HCD compared to ND, TRTSM and ZACAH extracts treatment groups (p< 0.05). The proteins levels of nitric oxide (NO) and tissue-type plasminogen activator (t-PA) were significantly downregulated while the tissue factor (TF) and plasminogen activator inhibitor-1 (PAI-1) protein concentrations were upregulated in the HCD group compared to ND, TRTSM and ZACAH extracts treatment groups (p<0.05). The mRNA expression of endothelial prothrombotic, coagulation related genes and the genes of the fibrinolytic system, including TF, PAI-1 and thrombin-activatable fibrinolysis inhibitor (TAFI) were upregulated, whereas the expression of endothelial nitric oxide synthase (eNOS), tissue factor pathway inhibitor (TFPI) and t-PA genes were downregulated in the HCD group compared to ND, TRTSM and ZACAH extracts treatment groups (P<0.05). No significant difference was recorded between ZACAH extracts treatment groups, ND and TRTSM treatment groups at p<0.05. The extent of the relationship between related proteins and genes expression profile determined by bivariate Pearson's product-moment correlation coefficient (r) was positively correlated across the groups. The findings suggested that ZACAH extracts supplementation could ameliorate the dysfunctional endothelial, activated platelet, hepatic steatosis and molecular atherothrombotic changes in SD rats fed with HCD, and could be considered a potential candidate for the treatment of hyperlipidaemia-related atherothrombotic cardiovascular diseases.

Keywords: High cholesterol diet, atherothrombotic proteins and genes, ZACAH extracts,

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

PENCIRIAN SELULAR DAN MOLEKULAR TERHADAP PENANDA BERKAIT ATEROTROMBOSIS KE ATAS TIKUS SPRAGUE DAWLEY YANG DIBERI MAKAN DIET BERKOLESTEROL TINGGI DISUPLEMEN DENGAN EKSTRAK HERBA

Oleh

IBRAHIM KALLE KWAIFA

September 2021

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Penyakit kardiovaskular aterotrombotik adalah punca kematian yang paling lazim diseluruh dunia. Walaupun antiplatelet, antikoagulan, simvastatin dan lain-lain kumpulan ubat-ubatan berkaitan yang dipreskrip secara global untuk gangguan ini telah tersedia, sesetengahnya biasanya dikaitkan dengan beberapa kesan buruk. Intervensi berasaskan sumber semula jadi telah diperakui sebagai alternatif. Kajian ini menggunakan gabungan ekstrak herba untuk rawatan aterotrombosis dalam tikus Sprague Dawley (SD) yang diberi makan diet berkolesterol tinggi (HCD). Kajian itu menyiasat potensi terapeutik ekstrak herba; gabungan daripada; *Zingiber officinale* (halia), *Allium sativum* (bawang putih), *Citrus Limon* (lemon), *Malus Domestica* (epal) / cuka sari epal dan Madu (ZACAH) pada penanda berkaitan aterotrombosis secara selular dan molekular ke atas tikus SD yang diberi makan HCD. Pengenalpastian sebatian fitokimia utama yang terdapat dalam ekstrak ZACAH telah dilakukan dengan pemprofilan kromatografi cecair berprestasi tinggi-spektrofotometri jisim (UHPLC-MS) pada kedua-dua model negatif dan positif. Tiga puluh enam tikus SD jantan dibahagikan secara rawak kepada enam kumpulan mengikut jenis diet yang diberikan; diet biasa (ND), HCD, rawatan dengan simvastatin (TRTSM) pada kadar 10mg/kg mengikut berat badan (BW), rawatan dengan ekstrak ZACAH (TRT1) pada 1mg, 3mg (TRT2), dan 5mg (TRT3) sekilogram mengikut berat badan. Pada akhir minggu ke 12 eksperimen, tikus telah dikorbankan dan darah terkumpul telah dilakukan ujian profil lipid, ekspresi protein dan analisis ultrastruktur platelet dengan scanning electron microscope (SEM). Indeks aterogenik (AI) dan peratus perlindungan dikira berdasarkan keputusan yang diperolehi daripada profil lipid. SEM juga digunakan untuk memeriksa perubahan ultrastruktur endothelial aorta. Aorta dan tisu hati juga telah digunakan untuk pemeriksaan histopatologi menggunakan pewarnaan haematoxylin & eosin (H & E) dan trichrome masson (MT) noda. Tisu-tisu ini juga di proses untuk meneliti ekspresi mRNA bagi gen berkaitan aterotrombosis metabolisme lipid, protrombotik dari endothelial dan gen berkaitan pembekuan, dan gen sistem fibrinolitik. Sepuluh sebatian fitokimia

berkaitan yang terdapat dalam ekstrak ZACAH telah dikenal pasti, termasuk gingerol (masa pengekalan (RT); 18.62, sebatian%; 5.6), hesperidin (11.19, 12.1), naringin (10.07, 13.1), sulindac (13.96, 9.7), scoparone (15.86, 8.0), hesperetin (11.18, 12.1), rutin (9.90, 13.2), limonin (17.87, 6.2), asid karboksilik (3.30, 18.9) dan asid sitrik (2.18, 20). Peningkatan BW dan pengambilan makanan telah turut direkodkan. Perbezaan yang ketara diperhatikan dalam kumpulan HCD berbanding kumpulan rawatan ekstrak ND, TRTSM dan ZACAH ($p<0.05$). Jumlah kolesterol (TC), trigliserida (TG) dan lipoprotein berketumpatan (LDL) rendah telah meningkat dengan ketara dan penurunan lipoprotein berketumpatan tinggi (HDL) telah diperhatikan dalam kumpulan HCD berbanding kumpulan rawatan akstrak ND, TRTSM dan ZACAH ($p<0.05$). Perbezaan ketara diperhatikan dalam AI HCD berbanding kumpulan rawatan ekstrak ND dan ZACAH ($p<0.05$). Peratus perlindungan telah dipertingkatkan pada TRTSM (18%), TRT1 (55.6%), TRT2 (59.7%) dan TRT3 (72.8%) dalam cara yang bergantung kepada dos. Analisa SEM menunjukkan aterotrombosis yang teratur, petambahan sel otot licin dalam intima, dan platelet yang teraktif dengan ketara dalam kumpulan HCD. Pemeriksaan histopatologi menunjukkan peningkatan ketara dalam nisbah intima-media, peningkatan gentian kolagen dan steatosis hepatik ketara dalam kumpulan HCD berbanding kumpulan rawatan ekstrak ND, TRTSM dan ZACAH ($p<0.05$). Ekspresi mRNA metabolisme lipid gen, *termasuk 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMG-CoA-R), proprotein convertase subtilizing Kexin-9 (PCSK-9) and sterol regulatory element-binding protein-2 (SREBP-2)* dikawal selia manakala ekspresi gen reseptor lipoprotein berketumpatan rendah (LDL-R) berkurangan dalam HCD berbanding kumpulan rawatan ekstrak ND, TRTSM dan ZACAH ($p<0.05$). Tahap protein oksida nitrat (NO) dan pengaktif plasminogen jenis tisu (t-PA) telah di bawah kawal selia dengan signifikan, manakala factor tisu (TF) dan kepekatan protein penghambat pengaktif plasminogen-1 (PAI-1) telah di atas kawal selia dalam kumpulan HCD berbanding kepada kumpulan rawatan ekstrak ND, TRTSM dan ZACAH ($p<0.05$). Ekspresi mRNA protrombotik endothelial, gen berkaitan pembekuan dan gen sistem fibrinolitik, termasuk TF, PAI-1 dan *thrombin-activatable fibrinolysis inhibitor* (TAFI) telah di dikawal selia, manakala ekspresi gen mRNA *endothelial nitric oxide synthase* (eNOS), perencat laluan faktor tisu (TFPI) dan t-PA berkurangan dalam kumpulan HCD berbanding kumpulan rawatan ekstrak ND, TRTSM dan ZACAH ($P<0.05$). Tiada perbezaan yang ketara direkodkan antara kumpulan rawatan ekstrak ZACAH, kumpulan rawatan ND dan TRTSM pada $p<0.05$. Tahap hubungan antara profil ekspresi protein dan gen yang berkaitan yang ditentukan oleh pekali korelasi momen-produk bivariat Pearson (r) telah dikaitkan secara positif merentas kumpulan. Penemuan ini mencadangkan bahawa suplemen ekstrak ZACAH berupaya memperbaiki endothelial disfungsi, hiperaktif platelet, steatosis hepatik dan perubahan aterotrombotik molekul dalam tikus SD yang diberi HCD dan mungkin dianggap sebagai pilihan yang berpotensi untuk rawatan penyakit kardiovaskular aterotrombotik yang berkaitan dengan hiperlipidaemia.

Kata kunci: Diet tinggi kolesterol, protein dan gen aterotrombotik, ekstrak ZACAH

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This thesis was submitted to the Senate of the Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Doctor of Philosophy. The members of the Supervisory Committee were as follows:

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8-OHdG	8-Hydroxy-2-Deoxyguanosine
AA	Arachidonic Acid
AB	Antibody
ABCA1	ATP-Binding Cassette Transporter A1
ABCG1	ATP-Binding Cassette Transporter G1
ABI	Ankle-Brachial Index
ABPI	Ankle-Brachial Blood Pressure Index
Abs	Absorbance
ACAS	Acetyl CoA Synthase
ACS	Acute Coronary Syndrome
ACV	Apple Cider Vinegar
AD	Adventitia
ADAMA	Asymmetric Dimethyl-L-Arginine
ADP	Adenosine Diphosphate
AGES	Advanced Glycation End-Product
AHA	American Heart Association
ALP	Alkaline Phosphatase
ALT	Alanine Transferase
AMI	Acute Myocardial Infarction
AMPK	Activated-Mitogen Protein Kinase
Ang II	Angiotensin-II
ANOVA	Analysis of Variance
AP-1	Activated Protein-1

APC	Activated Protein C
Apo AI	Apolipoprotein AI
Apo B48	Apolipoprotein B [(%)]
Apo B100	Apolipoprotein B [100 (%)]
Apo C	Apolipoprotein C
Apo E	Apolipoprotein E
ARAS	Atomic Resonance Absorption Spectrometry
AST	Aspartate aminotransferase
AT	Arterial Thrombosis
ATIII	Antithrombin III
ATE	Arterial Thromboembolism
ATP	Adenosine Triphosphate
BD	Bile Ducts
BFGF	Basic Fibroblast Growth Factor
BH_4	Tetrahydrobiopterin
BM	Bone Marrow
BMI	Body Mass Index
BP	Blood Pressure
Ca^{2+}	Calcium Ion
CAC	Coronary Artery Calcium
CAD	Coronary Arterial Disease
CaMKK-2	Ca^{2+}+ Calmodulin Dependent Protein Kinase Kinase-2
CAMs	Cells Adhesion Molecules
CARM-1	Coactivator-Associated Methyltransferase-1

CCL	Chemokine (C-C Motif) Ligand
CCL_4	Carbon Tetrachloride
CD	Cluster of Differentiation
CDCP	Centre for Disease Control and Prevention
cDNA	Complementary Deoxyribonucleic Acid
CD40L	CD40 Ligand
C/EBPs	CCAAT/Enhancer-Binding Proteins
CE	Cholesterol Ester
CETP	Cholesterol Ester Transferring Protein
cGMP	Cyclic Guanidine Monophosphate
CHDs	Coronary Heart Diseases
CM	Chylomicron
CO_2	Carbon Dioxide
COX	Cyclooxygenase
Cr	Creatinine
CRP	C-Reactive Protein
CS	Cigarette Smoking
CV	Coefficient of Variation
CVDs	Cardiovascular Diseases
DEPC-treated water	Diethylpyrocarbonate-treated water
DIC	Disseminated Intravascular Coagulopathy
DM	Diabetes Mellitus
DMIQE	Digital Minimum Information for Publication of Quantitative RT-PCR Experiments
DNL	*De Novo* Lipogenesis

DPX	Distyrene Plasticizer and Xylene
DVT	Deep Vein Thrombosis
DVTE	Deep Vein Thromboembolism
DW	Distilled Water
ECs	Endothelial Cells
ECM	Extracellular Matrix
EDHF	Endothelium-Derived Hyperpolarizing Factor
EDTA	Ethylenediaminetetraacetic Acid
EGF	Epidermal Growth Factor
ELISA	Enzyme-Linked Immunosorbent Assay
EMCV	Encephalomyocarditis
EMCs	Electron Microscopes
eNOS	Endothelial Nitric Oxide Synthase
EPCR	Endothelial Protein C Receptor
EPI	Extrinsic Pathway Inhibitor
ESI	Electrospray Ionization
ET1	Endothelin-1
FCHL	Familial Combined Hyperlipidaemia
FDA	Food And Drugs Administration
FDPs	Fibrin Degradation Products
FFAs	Free Fatty Acids
FGF	Fibroblast Growth Factor
FH	Family History
FHC	Familial Hypercholesterolemia

FHL	Familial Hyperlipidaemia
FMD	Flow Mediated Dilation
FN	Fibrinogen
FPA	Fibrinopeptide A
FPB	Fibrinopeptide B
FPSK	Fakulti Perubatan Dan Sains Kesihatan
FI	Fibrinogen
FII	Prothrombin
FIII	Thromboplastin (Tissue Factor)
FIV	Calcium Ion
FV	Labile Factor/ Proaccelerin
FV Leiden	Factor V Leiden
FVI	Accelerin
FVII	Stable Factor/ Proconvertin
FVIII	Anti-Haemophilia A Factor
FIX	Christmas Factor/ Anti-Haemophilia B
FX	Stuart Prower Factor
FXI	Anti-Haemophilia C Factor/ Plasma Thromboplastin Antecedent
FXII	Hageman Factor
FXIII	Fibrin Stabilizing Factor
GIT	Gastrointestinal Track
GOT	Gene of Interest
GP	Glycoprotein
GPIb	Glycoprotein Ib

GPx	Glutathione Peroxidase
GPVI	Glycoprotein VI
GSH	Glutathione
GWAS	Genome-Wide Association Study
HA	Hepatic Artery
Hb	Haemoglobin
HBP	High Blood Pressure
HBV	Hepatitis B Virus
HCD	High Cholesterol Diet
HCV	Hepatitis C Virus
HDL	High Density Lipoprotein
HDL-C	High Density Lipoprotein-Cholesterol
H & E	Haematoxylin and Eosin
HESI	Heat Electrospray Ionisation
HF	History of The Family
HFD	High Fat Diet
HGF	Hepatocyte Growth Factor
HIV	Human Immune Virus
HL	Hepatic Lipase
HMDS	Hexamethyldisilane
HMG-CoA-R	3-Hydroxy-3-Methylgutaryl Coenzyme A-Reductase
HMWK	High Molecular Weight Kininogen
HOCl	Hypochlorous Acid
HPLC	High Performance Liquid Chromatography

HPS	Hormone Sensitive Lipase
HRP	Horse Reddish Peroxidase
HSPG	Heparan Sulphate Proteoglycans
H_2O_2	Hydrogen Peroxide
H_2S	Hydrogen Sulphide
HT	Hormone Therapy
5-HT	5-hydroxytryptamine
I	Intima
ICAM-1	Intercellular Adhesion Molecule-1
IDL	Intermediate Lipoprotein
IGF-1	Insulin-Like Growth Factor-1
IHD	Ischaemic Heart Disease
IKK	Inhibitor of Kappa B Kinase
IL	Interleukin
IL-1β	Interleukin-1β
IL-6	Interleukin-6
IL-10	Interleukin-10
IMT	Intimal Media Thickness
INF-γ	Interferon-Gamma
iNOS	Inducible Nitric Oxide Synthase
INR	International Normalised Ratio
IS	Ischemic Stroke
JAM	Junctional Adhesion Molecule
JNK – c-Jun	C-Jun N-Terminal Kinase

KLF	Kruppel-Like Factor
L	Lumen
LC	Liquid Chromatography
LCAT	Lectin-Cholesterol-Acyltransferase
LC-MS	Liquid Chromatography- Mass Spectrophotometry
LD	Lipid Droplet
LDL	Low Density Lipoprotein
LDL-C	Low Density Lipoprotein-Cholesterol
LDL-R	Low Density Lipoprotein-Receptor
LOX-1	Lectin-Like Oxidized LDL Receptor-1
Lp(a)	Lipoprotein(a)
LPL	Lipoprotein Lipase
LRP-1	LDL-Receptor Related Protein-1
M	Media
MAPK	Mitogen-Activated Protein Kinase
MAPKP	Mitogen-Activated Protein Kinase Pathway
MCP-1	Monocyte Chemoattractant Protein-1
M-CSF	Monocyte Colony Stimulating Factor
MDA	Malondialdehyde
MI	Myocardial Infarction
MIP-1α	Macrophages Inflammatory Prtien-1α
MiRNAs	Micro-RNAs
MMP-1	Matrix Metalloproteinase-1
MMP-2	Matrix Metalloproteinase-2

MMP-9	Matrix Metalloproteinase-9
MPV	Mean Platelet Volume
MS	Mass Spectrophotometry
MT	Masson's Trichrome
NAFLD	Non-Alcoholic Fatty Liver Disease
NASH	Non-Alcoholic Steatohepatitis
NCBI	National Centre for Biotechnology Information
ND	Normal Diet
NF-KB	Nuclear Factor Kappa-Light-Chain Enhancer of Activated B-Cells B
NHMS	National Health and Morbidity Survey
NIH	National Institutes of Health
NLM	National Library of Medicine
NO	Nitric Oxide
NS	Normal Saline
NSAID	Nonsteroidal Anti-inflammatory Drugs
OH	Hydroxyl
ONOO-	Peroxyniitrite
Ox-LDL	Oxide-Low Density Lipoprotein
Ox-LDL-Th	Oxide-Low Density Lipoprotein-T-Helper Lymphocyte
PACE-4	Proprotein Convertase Cleaving Enzyme-4
PADs	Peripheral Arterial Diseases
PAF	Platelet-Activating Factor
PAI-1	Plasminogen Activator Inhibitor-1
PAP	Physiologic Anticoagulation Pathway

PAPase	Phosphatidate Phosphohydrolase
PAR	Protease-Activated Receptor-1
PAR-1	Protease Activator Receptor-2
PBS	Phosphate Buffer Saline
PC	Protein C
PC-1	Proprotein Convertase-1
PCL	Prostacyclin
PCSK-9	Proprotein Convertase Subtilisin/Kexin Type-9
PDI	Protein Disulphide Isomerases
PDGF	Platelet-Derived Growth Factor
PE	Pulmonary Embolism
PECAM-1	Platelet Endothelia Cell Adhesion Molecule-1
PF4	Platelet Factor-4
PGH_2	Prostaglandin H_2
PGL	Prostaglandin
PGs	Proteoglycan
PKA	Protein Kinase A
PKR	Protein Kinase-R
PPARs	Peroxisome Proliferator-Activated Receptors
PS	Protein S
PUFAs	Polyunsaturated Fatty Acid
PVDs	Peripheral Vascular Diseases
QTOF	Quadrupole Time of Flight
R^2	Coefficient of Determination

r	Correlation Coefficient
RANTES	Regulated on Activating, Normal T-Cell Expressed and Secreted
RAS	Rat Sarcoma
RBCs	Red Blood Cells
Rho	Ras Homologous
RNA	Ribonucleic Acid
RNS	Reactive Nitrogen Species
ROS	Reactive Oxygen Species
rpm	Revolution Per Minute
RT-qPCR	Real-Time Quantitative Polymerase Chain Reaction
SKI-1	Subtilisin Kexin Isoenzyme-1
SLE	Systemic Lupus Erythematosus
SMCs	Smooth Muscle Cells
SNPs	Single Nucleotide Polymorphisms
SO_2	Sulphur Dioxide
SPSS	Statistical Package for Social Sciences
SRs	Scavenger Receptors
SR-B1	Scavenger Receptor B Type 1
SREBP-2	Sterol Regulatory Element Binding Protein-2
Svcam-1	Soluble Vascular Cell Adhesion Molecule-1
TAE	Tris-Acetate-EDTA
TAFI	Thrombin-Activatable Fibrinolytic Inhibitor
TBE	Tris Borate-EDTA
TC	Total Cholesterol

TCFA	Thin-Cap Fibroatheroma
T2DM	Type-II Diabetes Mellitus
TEM	Transmission Electron Microscope
TF	Tissue Factor
TF-MPs	Tissue Factor-Bearing Microparticles
TFPI	Tissue Factor Pathway Inhibitor
TG	Triglycerides
TGF-B R-II	Transforming Growth Factor-B Receptor-II
TGRP	Triglyceride-Rich Lipoprotein Particles
Th	T-Helper Cells
TIA	Transient Ischaemic Attack
TLRs	Toll-Like Receptors
TM	Thrombomodulin,
TNF-α	Tumour Necrosis Factor-Alpha
TNF-1β	Tumour Necrosis Factor-1β
t-PA	Tissue-Type Plasminogen Activator
TPC	Total Phenolic Content
TRs	Thromboxane Receptors
TRT1	Treatment at 1mg/Kg 0f Body Weight
TRT2	Treatment at 3mg/Kg 0f Body Weight
TRT3	Treatment at 5mg/Kg 0f Body Weight
TRTSM	Treatment with Simvastatin at 10mg/Kg 0f Body Weight
T-TM	Thrombin-Thrombomodulin
TXA2	Thromboxane A_2

TXB2	Thromboxane B2
UHPLC	Ultra-High Pressure Liquid Chromatography
ulvWF	Ultra-Large von Willebrand Factor
uPA	Urokinase Plasminogen Activator
uPA-R	Urokinase Plasminogen Activator-Receptor
VCAM-1	Vascular Cell Adhesion Molecule-1
VEGF	Vascular Endothelial Growth Factor
VKA	Vitamin K-Antagonists
VKAs	Vitamin K-Dependent Anticoagulants
VLDL	Very Low-Density Lipoprotein
VLDL-C	Very Low-Density Lipoprotein Cholesterol
VSMC	Vascular Smooth Muscle Cells
VT	Venous Thrombosis
VTE	Venous Thromboembolism
vWF	von Willebrand Factor
WHO	World Health Organization
WPB	Weibel-Palade Bodies
α_2-AP	α_2-Antiplasmin
ZACAH	Zingiber Officinale (Ginger), Allium Sativum (Garlic), Citrus Limon (Lemon), Malus Domestica (Apple)/ Apple Cider Vinegar and Honey.

CHAPTER 1

INTRODUCTION

1.1 Atherothrombosis

Atherothrombosis is an atherosclerotic lesion with thrombus formation and has been recognised as the major cause of ischemic heart disease and other cardiovascular diseases (CVDs), associated with global deaths (Grover & Mackman, 2020; Roth et al., 2020). The initial pathophysiology that gives rise to IHD is atherosclerosis, an inflammatory condition of the arterial vessels associated with the accumulation of lipids and metabolic modifications caused by several risk factors. Atherosclerosis is the underlying cause of CVDs characterized by plaque formation in the endothelial lumen. Atherosclerotic plaque is composed of accumulated lipids, cellular elements, including vascular smooth muscle cells (VSMCs), endothelial cells (ECs), immune mobilizing cells, such as monocyte, macrophage, T-cell and B-cell from blood circulation, calcium ions, and other formed blood elements (Shapiro & Fazio, 2017). Under normal physiology, cells are protected from the intracellular deposition of lipids by constantly regulated synthesis, through the influx and efflux of cholesterol. Lipids are organic compounds, insoluble in water, necessarily needed for normal metabolic processes. They are the basic components of the cell membrane, functioning as an energy reserve, participating in the absorption of fat-soluble vitamins, forming an essential part of various hormones, contributing effectively as co-factors, intracellular messengers, and maintaining the integrity of the cell membrane (Ahmed et al., 2021**;** Verma, 2016)**.** Accumulation of lipids in the bloodstream might be attenuated by the endothelium, which participates significantly in the regulation of blood flow through its anti-inflammatory, anticoagulant and profibrinolytic activities. Compromising these mechanisms could lead to excessive deposition of cholesterol, leading to organs toxicity, associated with apoptosis and enhanced necrosis. Excessive accumulation of lipids in the bloodstream could result in several metabolic conditions, including hyperlipidaemia and obesity (Verma, 2016)**.**

Existing report has demonstrated that hyperlipidaemia is associated with the increased serum concentrations of total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL), and a corresponding decrease in the serum level of high-density lipoprotein (HDL), in high cholesterol-induced SD rats (Fattepur et al., 2018). Hyperlipidaemia has been recognised as the most common risk factor to atherothrombotic CVDs, such as coronary heart diseases (CHDs), cerebral stroke, myocardial infarction (MI), and renal dysfunction (Karam et al., 2018; Badimon et al., 2012). Several factors, including vascular endothelial lumen, thrombogenicity, local haemorheology, systemic thrombogenicity, and fibrinolytic activities are known to mediate atherothrombotic propagation and formation (Asada, 2020). Arterial thrombi have been identified to contain aggregated platelets due to high blood velocity. However, established atherothrombosis from disrupted plaques may contain not only aggregated platelets but also a significant amount of fibrin. Plaque disruption facilitates both the activations of platelet and coagulation cascade at the injured vascular surface, leading to

a pronounced atherothrombotic process (Asada, 2020). Previous study has demonstrated high blood cholesterol and LDL levels after feeding SD rats with 4% cholesterol for four weeks (Balkanci et al., 2012). Therefore, a high cholesterol diet (HCD) could be utilized to develop high cholesterol SD rats model, targeting hyperlipidaemia (Rosenbaum & Chaudhuri, 2014). Several natural-based products have been used to treat various metabolic conditions, including CVDs (Kirichenko et al., 2020). Herbal extracts as natural sources contained *Zingiber officinale* (ginger), *Allium sativum* (garlic), *Citrus limon*_(lemon), *Malus domestica* (Apple)/ apple cider vinegar and honey (ZACAH extracts), formulated to treat high blood pressure (HBP) and reduce cholesterol levels. This study utilises the above-mentioned mechanisms to investigate the therapeutic potentials of ZACAH extracts on atherothrombosis-related markers in SD rats fed with a high cholesterol diet (HCD). At present, there is a lack of information on the therapeutic potentials of ZACAH extracts on hyperlipidaemia-related atherothrombotic CVDs. Therefore, this present study investigated the mechanisms of action of ZACAH extracts on cellular and molecular atherothrombosis-related markers in SD rats fed with HCD. The efficacy of the phytochemicals present in ZACAH extracts would be compared with simvastatin, to provide experimental evidence for utilizing ZACAH extracts, to treat hyperlipidaemia-related atherothrombotic complications.

1.2 Problem Statement

The incidence and severity of IHD and other atherothrombosis-related CVDs are grossly increasing worldwide (Karam et al., 2018). Pharmacological agents, including statin, antiplatelet and anticoagulant, are the gold standard drugs prescribed to treat hyperlipidaemia-related atherothrombotic CVDs. The hallmark of these drugs is to inhibit the excess accumulation of lipids, activation of platelets, endothelial cells (ECs), and coagulation cascade while promoting profibrinolytic activities by facilitating the clearance of TG-rich lipoprotein and enhancing endothelial nitric oxide bioavailability (Karam et al., 2017)**.** Although the present anti-atherothrombotic drugs available are safe and effective, the morbidity and mortality caused by atherothrombosis are still unacceptably high (Dias et al., 2018). Many of these drugs are mostly associated with several side effects (Khan et al., 2018**)**. Statin, such as simvastatin, a lipid-lowering agent, also known as 3-hydroxy-3-methyl-glutaryl coenzyme A reductase inhibitor, is associated with several side effects, including fever, headache, gastric irritation, myositis, hyperuricaemia, rhabdomyolysis, myalgia, renal and hepatic dysfunctions (Hussain et al., 2019; Fattepur et al., 2018; Khan et al., 2018). Acetylsalicylic acid, including aspirin, are antiplatelet synthetic drugs widely prescribed to treat inflammation, headache, fever and atherothrombosis-related CVDs (Heart et al., 2019). Aspirin, in particular, has been reported to inhibit cyclooxygenase (COX), a potent enzyme that catalyses prostaglandin formation by blocking the synthesis of thromboxane A2 (TXA2), an essential mediator of blood clotting (Karam et al., 2019a). However, aspirin and other related antiplatelet drugs were reported to give recurrent thromboembolic vascular events (aspirin intolerance), including dizziness, nausea, abdominal pain or patients may suffer from increased risk of bleeding (Heart et al., 2019**;** Karam et al., 2019b). Coumarin and its derivaties are class of vitamin K–dependent anticoagulants (VKAs). Warfarin is the most common anticoagulant agent currently in use. Coumarin and its derivatives are class of vitamin K–dependent anticoagulants (VKAs). Warfarin is the most common anticoagulant agent currently in use. It functions

to inhibit vitamin K epoxide reductase (VKOR), which is necessarily needed for the gamma-carboxylation of vitamin K-dependent factor, including factors II, VII, IX, X and protein C and S. Inhibition of vitamin K carboxylation triggers the decreased hepatic synthesis activity of clotting factors, leading to an anticoagulated state. Bleeding is the most common complication associated with warfarin therapy and is related to exponentially higher international normalised ratio (INR) values. The goal of the management is to reduce the INR back to a therapeutic safe level (Heart et al., 2019).

Existing reports have shown that plant extracts have analgesic, antioxidant, antibacterial, antihyperlipidemic, anti-inflammatory, and antitumor properties, while the documented evidence concerning the anti-atherothrombotic potentials of many plant extracts are still lacking (Kirichenko et al., 2020; Khan et al., 2018; Fattepur et al., 2018). Adequate clinical investigations and scientific validations are still lacking for the authentication and recommendation of the plant extracts, to be used in the treatment of hyperlipidaemia-related atherothrombotic CVDs (Balaji et al., 2016).

1.3 Study Justification

Treatment failure associated with synthetic-based therapies posed a challenge to the researchers to look for alternative medications. In this regard, the development of natural-based products to augment conventional synthetic drugs is essential. They are more effective in reducing the serum levels of TC, TG and LDL while elevating HDL serum levels and enhancing nitric oxide (NO) bioavailability (Newman & Cragg, 2016).

1.4 The objective of the Study

1.4.1 General Objective

To investigate the mechanisms of action of ZACAH extracts on cellular and molecular atherothrombosis-related markers in SD rats fed with a high cholesterol diet (HCD).

1.4.2 Specific Objectives

1. To identify the major phytochemicals present in ZACAH extracts by UHPLC-MS profiling and animal study
2. To determine the effects of ZACAH extracts on body and liver weights, food intake, lipid profile and hepatic histopathological changes in SD rats fed with HCD.
3. To examine the endothelial and platelet ultrastructural and histopathological changes in SD rats fed with HCD supplemented with ZACAH extracts.
4. To determine the mRNA expression profiling of lipid metabolism atherothrombosis-related genes in SD rats fed with HCD supplemented with ZACAH extracts.
5. To evaluate the levels of atherothrombosis-related proteins, the mRNA expression profiling of the endothelial prothrombotic, coagulation and fibrinolytic genes in SD rats fed with HCD supplemented with ZACAH extracts.
6. To correlate the activities of related proteins with the expression profile of atherothrombosis-related genes, and the genes expression pattern in SD rats fed with HCD supplemented with ZACAH extracts.

1.5 Research Hypothesis

ZACAH extracts have inhibitory effects on excess cholesterol, activated platelets and endothelial cells, abnormal coagulation and fibrinolytic system through modulation of the proteins and genes involved in lipid metabolism, endothelial prothrombotic, coagulation and fibrinolytic system.

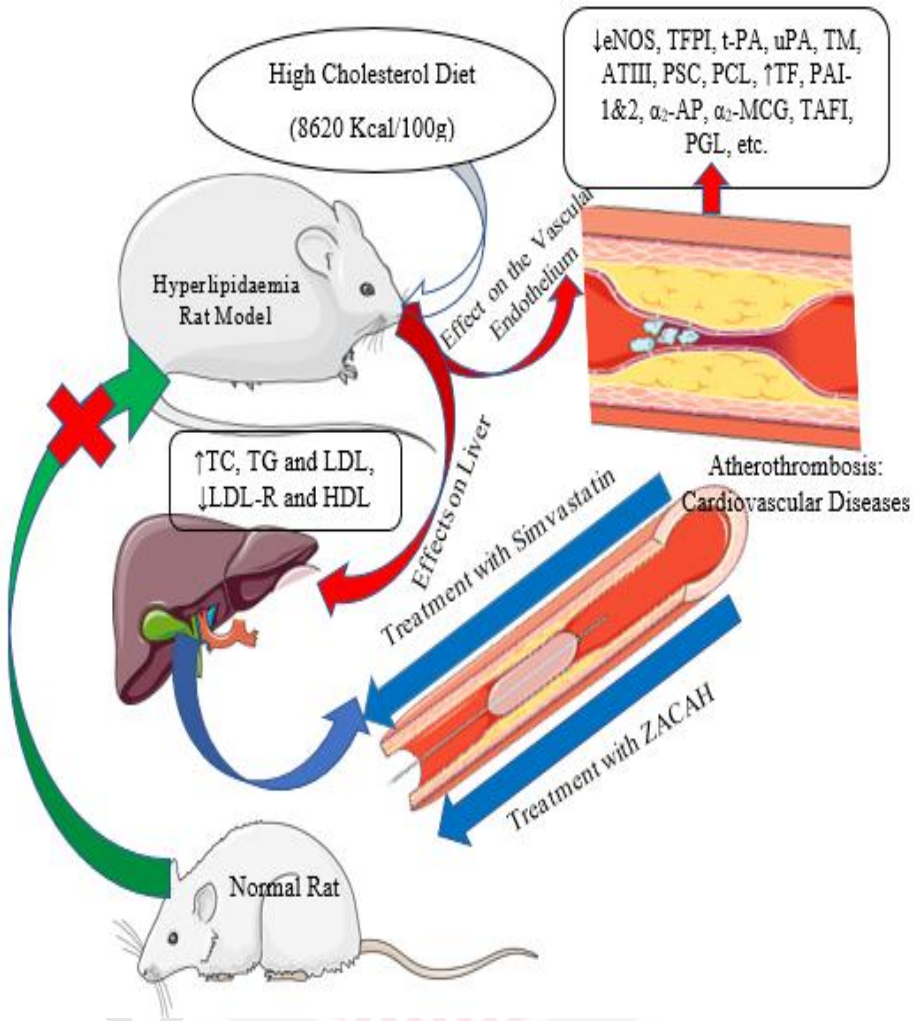

Figure 1.1 : Research Concept Map: Therapeutic potentials of ZACAH on atherothrombosis-related markers in SD rats fed with HCD

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